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Review article

Neurotransmitters and vulnerability of the developing brain ☆

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The immature human brain undergoes remarkable organizational changes during intrauterine and postnatal life. These changes create potential temporal 'windows' of selective vulnerability to damage. For example, the temporary germinal matrix is vulnerable to hemorrhage in the third trimester fetus and premature infant. The immature oligodendroglia present in developing white matter of the fetus are also vulnerable to injury producing periventricular leukomalacia. Similar changes take place in the synapses that make up the infant's neuronal circuitry. In human cerebral cortex, synapses are produced in greater than adult numbers by postnatal age 2 years and then reduced over the next decade. Over the same period receptors for glutamate, the most important excitatory neurotransmitter, change their characteristics to allow them to participate in activity dependent synaptic plasticity. For example, the immature *N*-methyl-D-aspartate (NMDA) type glutamate receptor/channel complex, which plays important roles in long term potentiation (LTP), neuronal migration and synaptic pruning, contains subunits that allow the channel to be opened more easily for a longer period than adult channels. These developmental changes make the immature brain selectively vulnerable to NMDA receptor overstimulation that can occur during hypoxia-ischemia and other insults. Several types of neuropathology in the developing brain can be understood on the basis of these organizational principles.

Keywords: Glutamate; NMDA; Neurotransmitter; Synapse; Development

1. INTRODUCTION

The immature brain undergoes remarkable changes in organization during fetal and postnatal development [1]. Some structures such as myelination of pathways are added progressively throughout postnatal development so that the mature brain contains white matter that the younger brain lacks. However, the developing brain also contains structures and cellular elements that are absent in the older brain. A good example is the germinal matrix that is a site of neurogenesis and gliogenesis during early and mid gestation. This structure has virtually disappeared by the end of a term pregnancy but in the preterm infant it can be a site of intracranial hemorrhage [2]. Another example is the fact that the fetal brain generates more neurons than it will need for adult life. The final population of neurons in the brain is the sum of neuronal production and neuronal cell death, partly through the process of programmed cell death or apoptosis [3]. A surplus of interneuronal connections is also generated postnatally and then pruned during childhood. Studies by Huttenlocher in the developing human brain indicate that approximately twice as many synapses are present in certain parts of the cerebral cortex during early postnatal life than during adulthood [4]. The neonatal brain also contains a temporary 'subplate zone' between the immature cerebral cortex and white matter containing fetal neurons and immature synapses that disappear after the sixth postnatal month [5]. Therefore, the immature brain differs from the adult not only because it lacks some of the structures that are prominent in the adult brain, such as myelin, but also because it possesses certain temporary structures that regress postnatally. These neurobiologic observations are consistent with those of psychologists who have suggested that young infants and children may have enhanced behavioral abilities that disappear or are less apparent later in life [6]. The develop-

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ing brain, more than most other organs in the body, is organizationally different than the final mature nervous system.

2. DEVELOPMENTAL CHANGES CREATE SPECIAL PATTERNS OF VULNERABILITY

These facts are quite interesting from the standpoint of basic neurobiology and comparative anatomy but they also appear to be important for understanding patterns of injury in the developing brain. The implication of these observations is that the immature brain can be vulnerable in locations that lack sensitivity to injury later on. For example, the fragile capillaries in the germinal matrix of the preterm infant create vulnerability to intracranial hemorrhage that diminishes later in life [2]. Another interesting example is the vulnerability of the immature white matter to the pattern of injury called periventricular leukomalacia (PVL) [7]. Although more mature white matter can at times be sensitive to inflammatory injury, the developing white matter of the human prior to 32 weeks gestation is especially sensitive to damage from hypoxic and ischemic injury and metabolic insults [8]. These developmental windows of vulnerability are based on both cellular and vascular factors. From a vascular standpoint, the developing white matter can be considered to be in the center of a watershed region that can be deprived of blood if the infant loses pressure in the cerebral vasculature [9]. The vulnerability has also been shown to be based on the sensitivity of immature oligodendroglia [7]. These immature cells that form myelin appear to be sensitive to oxidative stress and injury from excessive free radical formation. The selective vulnerability of these cells from oxidative stress may contribute to injury to white matter from non-ischemic factors including bacterial endotoxin [10]. The temporary germinal matrix and the very immature oligodendroglia create windows of vulnerability of the preterm brain to damage. The morphologic characteristics and location of these structures can be nicely correlated with the location of brain damage and the clinical neurologic patterns of injury in older children and adults [8].

3. POSTNATAL CHANGES IN SYNAPTIC DEVELOPMENT

These two examples of selective vulnerability are taken from the preterm period of gestation but recent evidence suggests that certain patterns of damage in the infant at term and in postnatal life can also be understood in terms of the reorganizational events in the brain [8]. As the vulnerability of the developing white matter to hypoxia and ischemia tapers off after 32 weeks gestation, the vulnerability of the large masses of gray matter in the brain, especially the cerebral cortex and the basal ganglia, increases towards term and for several months of age postnatally [11]. The most

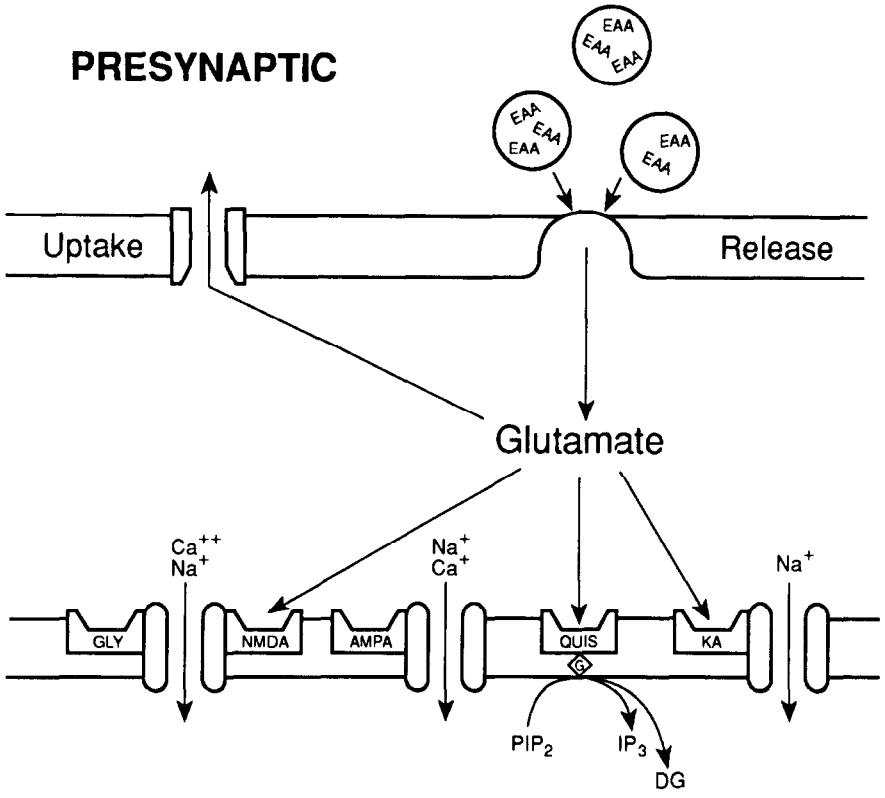

Fig. 1. Schematic diagram of glutamate synapses. Glutamate (EAA: excitatory amino acids) is released from the nerve terminal and can interact with several different glutamate receptor subtypes. The NMDA type receptor, with glycine (Gly) as a coagonist, opens a channel that fluxes sodium and calcium. The AMPA receptor operates a predominantly sodium fluxing channel. Glutamate in the conformation of quisqualate (QUIS) stimulates breakdown of phosphoinositide (PIP_2) to inositol triphophate (IP_3) and diacylglyceriol (DG) at a metabotropic receptor. (Reprinted with permission from: Haddad G, Lister G. *Tissue oxygen deprivation*. New York: Marcel Dekker, 1995.)

prominent developmental events occurring at this time are the proliferation of axonodendritic connections at synapses. The proliferation of synapses postnatally correlates with the trend of infants in the first 2 years of life to increase their cerebral glucose metabolic rate in the brain peaking at about twice the adult levels at 2 years of age [12]. The elaboration of synapses and development of the energy requiring electrogenic ionic pumps needed to maintain synaptic activity are responsible for some of this increase in metabolic rate.

4. IMMATURE SYNAPSES MAKE THE BRAIN VULNERABLE TO 'EXCITOTOXICITY'

Recent evidence suggests that some neurotransmitters and neurotransmitter receptors located on synaptic terminals also change their organization dramatically along with the proliferation of synapses. [13] These changes may be responsible for changes in vulnerability to injury occurring at this stage. The neurotransmitters most closely linked to the vulnerability of the brain to neuronal injury are the excitatory amino acids, primarily glutamate, aspartate and glycine. Excessive excitation, referred to as excitotoxicity, can stimulate ionic currents through ion channels in synaptic membranes that are capable of overwhelming and destroying neurons [14,15]. This synaptic 'overload' is especially likely to occur during periods of ischemia or other types of energy failure when excessive amounts of excitatory neurotransmitters are released but compensatory rescue mechanisms located in the neuronal membranes are underpowered.

To understand the concept of excitotoxicity as it relates to the developing brain it is worthwhile to review some basic features of excitatory and inhibitory synapses in the brain. As many as 60–70% of the synapses in the brain utilize glutamate, a dicarboxylic acidic amino acid, as their primary neurotransmitter [16]. When released from the presynaptic nerve terminal, glutamate is able to fit comfortably into several different conformations matching the receptors on several kinds of excitatory postsynaptic receptors (Fig. 1). Glutamate analogues that have rigid structures have been found to bind to specific glutamate receptor subtypes with great affinity. For example, the so-called *N*-methyl-D-aspartate (NMDA) receptor is characterized by having a high affinity for the rigid glutamate analog NMDA. Three kinds of ionotropic receptors for NMDA, AMPA (α-amino-3-hydroxy-5-methylisoazole-4-propionic acid) and kainic acid have been identified, each with different physiologic characteristics [17]. Another class of glutamate receptors called metabotropic receptors regulate the formation of either cyclic AMP or phosphoinositide intracellular second messengers [18]. These receptors are used throughout the phylogenetic tree and appear to have been exploited as neurotransmitters fairly early during evolution [19]. For example, the neuromuscular junction of certain insects uses a type of metabotropic glutamate receptor to mediate muscle contraction. Glycine, glutamate, aspartate, major excitatory transmitters and γ-aminobutyric acid (GABA), the major inhibitory transmitter, are among the simplest and most abundant amino acids.

The major inhibitory transmitter GABA generally works in a complementary fashion with glutamate and becomes

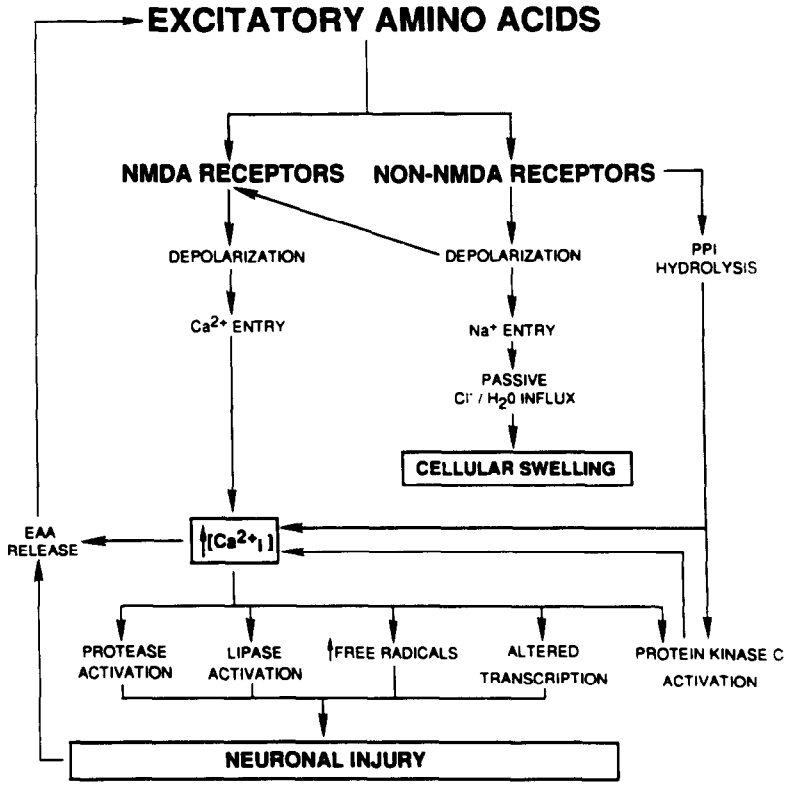

Fig. 2. Cascade of events that mediate excitotoxic neuronal injury through overstimulation of NMDA and non-NMDA glutamate receptors. Elevation of intracellular calcium is responsible for activating several enzyme mediated processes that destroy neurons. (Reprinted with permission from: Haddad G, Lister G. *Tissue oxygen deprivation*. New York: Marcel Dekker, 1995.)

activated to prevent excessive propagation of excitatory postsynaptic potentials [20]. GABA hyperpolarizes neuronal membranes by enhancing the flux of chloride through GABA mediated channels. It is noteworthy that GABA is produced from glutamate by decarboxylation through the enzyme glutamate dicarboxylase. This is a pyridoxal phosphate dependent enzyme that can be defective in a genetic metabolic form of refractory seizures [21]. In this disorder, pyridoxine dependence, excessive concentrations of glutamate accumulate and there is a reduced concentration of GABA resulting in refractory seizure disorder.

5. EXCITOTOXICITY IS TRIGGERED BY HYPOXIA-ISCHEMIA AND OTHER INSULTS

Excitotoxicity can occur when glutamate causes excessive amounts of calcium and sodium to traverse neuronal membranes when the mechanisms that normally control intracellular concentrations of ions are inactivated [22]. Hypoxia-ischemia, hypoglycemia and trauma can trigger accumulation of a high concentration of glutamate in the brain's extracellular fluid space [23,24]. These levels result from a combination of presynaptic release of glutamate and reduced activity or reversal of the glutamate reuptake pump that normally reduces extracellular glutamate following neuronal excitation [25]. Release of free fatty acids such as arachidonic acid from neuronal membranes appears to play a role in inhibiting the glutamate reuptake pump. Along with high levels of extracellular glutamate, NMDA type channels open when depolarization of neuronal membranes allows magnesium ions to leave the channel [26]. The NMDA type glutamate receptor fluxes a great deal of calcium and its slow inactivation produces prolonged increases in intracellular calcium. Overactivation of the NMDA receptor appears to be particularly dangerous for neurons that possess these receptors and channels.

Calcium appears to be the most immediately toxic chemical, as shown in Fig. 2, and is responsible for activating a cascade of intracellular enzymes that can virtually dissolve the neuron [13]. Important intracellular mechanisms that handle calcium include the endoplasmic reticulum and the mitochondria. Intracellular levels of calcium are controlled, in part, by receptor mediated release of calcium from the endoplasmic reticulum by inositol phosphates. The ability of mitochondria to sequester intracellular calcium is affected by available energy and by concentrations of sodium so that excessive flow of sodium into the neuron may add to the toxicity of NMDA receptor channel opening [27]. The most lethal neuronal injuries are those in which there is a large excess of extracellular glutamate along with a 'power shortage' that reduces the efficiency of mitochondrial mechanisms. One important neurotoxic effect of elevated intracellular calcium is to activate nitric oxide synthase through a calcium/calmodulin dependent mechanism to produce the free radical nitric oxide [28]. Nitric oxide can enhance release of neurotransmitters and can form peroxynitrite molecules that attack neuronal membranes. Recent evidence suggests that the excitotoxicity contributes to cell death through a mixture of necrotic and 'apoptotic' mechanisms that involve activation of intrinsic cell death programs [29]. Generation of free radicals of oxygen appear to play a role in both types of cell death [30,31]. Dissection of the specifics of cell death triggered by glutamate is an important area of investigation that may lead to strategies for intervening in the cascade of events that kill neurons.

6. IMMATURE EXCITATORY AMINO ACID RECEPTORS ARE MORE ACTIVE THAN ADULT FORMS

The distribution, electrophysiology and molecular characteristics of excitatory amino acid receptors change markedly throughout brain development and these changes strongly influence the brain's vulnerability to injury [13]. The distribution of glutamate receptor subtypes, the kinetics of channels and enzyme activities at different ages and the activity of protective mechanisms including the ability to neutralize free radicals can be modified developmentally with great effect on the outcome of injury. For example, it was noted several years ago that NMDA mediated excitatory postsynaptic potentials were larger in the visual neocortex of kittens compared to adult cats [32]. The density of cortical NMDA receptors is also higher in the early postnatal period of rats than in adulthood, suggesting that there is an overshoot in the number of these receptors followed by pruning later in development [13,33,34]. The activity of phosphoinositide hydrolysis activated by metabotropic glutamate receptor stimulation is approximately 10-fold higher in neonatal cerebral cortex of rat compared to adults [35]. It is also noteworthy that one metabotropic receptor subtype linked to phosphoinositide turnover, the $MGluR_5$ receptor, is expressed in greater than adult numbers in the rat somatosensory barrel field cortex at 10 days of age [36].

7. MOLECULAR BIOLOGIC STUDIES DEMONSTRATE CHANGES IN EXCITATORY AMINO ACID RECEPTORS

Molecular biologic studies suggest that the electrophysiologic changes in NMDA receptors during development can be correlated to changes in subunits making up the immature NMDA receptor channel complexes [37]. The immature channels are different from those in the adult and are chemically constructed to conduct greater amounts of calcium than mature channels [38,39]. In addition to conducting more calcium, the channels assembled from the immature subunits are more easily stimulated by glycine, a co-agonist with glutamate, and have less ability to be blocked by magnesium

Table 1 *Features of NMDA receptors in the neonatal period*

Prolonged duration of NMDA mediated excitatory postsynaptic potential (EPSP) [40]
Reduced ability of magnesium to block EPSP [41,42]
Fewer polyamine binding sites [43]
Greater sensitivity to glycine enhancement of NMDA EPSP [44,45]
Switch from NR1/NR2B to NR1/NR2A subunits [44,45]
Higher density of NMDA receptors in postnatal period [33,34]

than more mature channels [40–45] (Table 1). These developmental changes provide the immature brain with channels that have greater electrical excitability than those in the adult brain. They are more appropriate for the important roles that these receptors appear to play in brain development and plasticity. For example, NMDA receptors play a role in activity dependent plasticity which allows synaptic circuitry to be tuned in response to environmental stimulation [13]. The so-called 'ocular dominance shift' that occurs in mammals with closure of one eye allows the visual cortex to reallocate the assignment of visual cortex to the more active axons driven by the active, open eye. The NMDA receptor responds to increased activity with greater fluxes of calcium across the neuronal membrane, which in turn may serve as a tropic signal to recruit more active synapses to form permanent circuits. Similar activity dependent changes may operate to reassign sensory functions to somatotopically organized maps in somatosensory cortex [36] and to prune excess synapses [46]. This concept links the mechanisms that allow the brain to organize itself in response to environmental cues through excitatory mechanisms that also create vulnerability to injury at critical periods in development. This implies that certain regions of the brain that have enhanced glutamate mediated plastic mechanisms may also be vulnerable to excessive stimulation and damage during hypoxia-ischemia and other stresses.

8. CHANGES IN RECEPTOR / CHANNEL CHARACTERISTICS LINKED TO NEURONAL SELECTIVE VULNERABILITY

The concept linking patterns of selective vulnerability in the developing brain to programs for expression of excitatory amino acid receptors, channels and second messenger systems has been validated generally by experimental models of excitotoxicity in animal models. Microinjection of nanomolar quantities of the glutamate agonist NMDA into postnatal rats of different ages demonstrated that 7 day old pups are more vulnerable to brain damage compared to older and younger pups [13]. It is interesting that hypoxic-ischemic brain injury is also enhanced at 7 days of age in rats and electron microscopy demonstrated that the histopathology of NMDA mediated injury and hypoxic-ischemic injury are nearly identical [47]. Also, structures such as the cerebral cortex, corpus striatum and hippocampus are especially vulnerable to both excitotoxic and hypoxic-ischemic injury and also a contain large number of glutamate receptors [13,48]. NMDA antagonist drugs also display similar profiles of regional neuroprotection in these vulnerable areas that resembles their neuroprotective activity against hypoxia-ischemia [49]. Agonists for other glutamate receptor subtypes such as AMPA receptors and kainate receptors cause their own patterns of injury that peaks at stages of development different from overstimulation of the NMDA receptor [50–52]. These results suggest that certain special patterns of injury to neurons in the developing brain can be rationalized, at least in part, by understanding the age and anatomically specific expression patterns of excitatory amino acid receptors.

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